1 may be found at page 7, lines 30-32, page 25, lines 33-34, support for the recitation of "prodrug derivative" may be found at page 12, line 5 to page 16, line 20, and page 31, example 5 to page 32, example 7 etc., support for the recitation of "solid carrier" and "sterile liquid carrier" may be found at page 26, lines 13-31 and page 29, lines 18-27 etc., support for the recitation of "aerosol form" may be found at page 27, lines 18-20, support for the recitation of "salt form of EDU" may be found at page 9 and page 31, lines 5-24 etc. Claims 2, 72, and 74-75 are presented for reconsideration. Claim 1 is amended in scope consistent with the presently amended claims 2, 72 and 74-75.

The specification has been amended to correct certain typographical errors evident in the chemical structures appearing on pages 14-16.

Claims 2 and 72-74 remain rejected under 35 U. S. C. 102(b) as being anticipated by U.S. Patent 5,506,151 of Ito et al. The Examiner states that Ito anticipates claims 2 and 72-74 because Ito teaches the EDU compound in the presence of water (See col. 6, example 1). The Examiner further states that the recitation of intended use of the composition does not lend patentability to a known composition. In response, the Applicants have cancelled claim 73, amended claims 2, 72 and 74, and added a new claim 75.

Ito is directed to the use of secondary and tertiary amines, including EDU, in immunoassays to suppress non-specific reactions (col. 1, lines 5-14). Such suppression improves the accuracy and reliability of the quantitative determination of the formation of immunoreactant-complementary immunoreactant complexes such as antigen-antibody complexes. More specifically, EDU is discussed as "useful in suppressing non-specific reactions in immunoassays, particularly immunoassays wherein an immunoreactant is attached covalently or by adsorption to a solid support" (col. 3, lines 47-57).

In contrast, as discussed in the specification of the present application, the pharmaceutical composition comprising a pharmaceutically effective amount of EDU or its salt is to be administered to mammals, including a human, because of the bioactivity of the pharmaceutically acceptable composition to generally modulate an immune response (page 1, lines 15-18).

Claim 2 has been amended to recite a pharmaceutically effective amount of N-ethyl-N'-(3-dimethylaminopropyl) urea or a salt thereof in combination with a pharmaceutical acceptable solid carrier. Water is not a pharmaceutical acceptable solid carrier. Therefore, EDU compound in the presence of water in Ito does not anticipate claim 2. Additionally, the Examiner states that Ito teaches a composition in the solid state, in addition to the liquid composition (see col. 4, lines 30-35). The immunoreactant is adsorbed or covalently bound to a solid support. The solid support in Ito is used to support and bind the immunoreactant for determining the extent of immunoreactant-complementary immunoreactant/analyte interaction in the immunoassays. A non-specific reaction suppressor, such as EDU, can be added to either or both of the immunoreactant and the analyte being determined.

In contrast, the pharmaceutically acceptable solid carrier in the present invention is one or more solid substances which are combined with an active pharmaceutical ingredient in a manner, such as a tablet form, that is suitable for administration to a human or other animal. Therefore, solid support in Ito is different from pharmaceutically acceptable solid carrier in the present invention. For example, claim 5 of Ito recites a solid support of a latex particle wherein an immunoreactant is coupled onto the latex particle. This is clearly not a pharmaceutically acceptable solid carrier of the present invention. Since Ito does not teach or suggest a pharmaceutically acceptable solid carrier, Ito does not anticipate claim 2 of the present invention

under 35 U.S.C. 102(b). Applicants respectfully request that the Examiner withdraw this rejection.

Claim 72 has been amended to recite a pharmaceutically effective amount of N-ethyl-N'-(3-dimethylaminopropyl) urea or a salt thereof in combination with a pharmaceutically acceptable sterile liquid carrier. Water in the EDU solution of Ito is not a pharmaceutically sterile liquid carrier. Since Ito does not teach or suggest any pharmaceutically acceptable sterile liquid carrier, Ito does not anticipate claim 72. Thus, the rejection to claim 72 under 35 U. S. C. 102(b) as being anticipated over Ito should be withdrawn. Newly added claim 75, which is a dependent claim of claim 72, is also novel under 35 U.S.C. 102(b) over Ito reference accordingly. Further, claim 75 recites that the pharmaceutically acceptable sterile liquid carrier is isotonic, which is not suggested or taught by the Ito reference.

Claim 74 has been amended to recite an aerosol form of a pharmaceutically effective amount of N-ethyl-N'-(3-dimethylaminopropyl) urea or a salt thereof. The EDU of Ito is not in aerosol form. Therefore, Ito does not teach each and every element of claim 74. Claim 74 therefore possesses novelty under 35 U.S.C. 102(b) over Ito.

Accordingly, Applicants believe that claims 2, 72, and 74-75 are now in condition for allowance. Early and favorable action is respectfully requested.

It is believed that no fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
COHEN, PONTANI, LIEBERMAN & PAVANE

By _____

Kent H. Cheng, Reg. No. 33,849
551 Fifth Avenue, Suite 1210
New York, New York 10176
(212) 687-2770

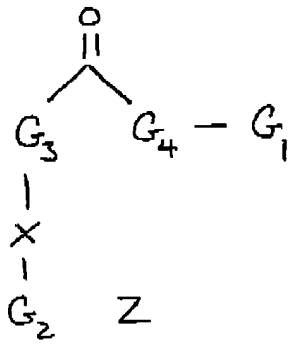
Dated: October 15, 2002

AMENDMENTS TO THE SPECIFICATION AND CLAIMS SHOWING CHANGES

In the Claims:

1. (Amended) A pharmaceutical composition, comprising:

[a pharmaceutical preparation of] a compound having the following formula:



or a prodrug derivative thereof, wherein G_1 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, aryl group or a heteroaryl group, wherein the aryl or heteroaryl is a ring having 5, 6 or 7 atoms, and wherein at least one atom of the heteroaryl is selected form the group consisting of a sulfur, a nitrogen, and an oxygen atom, wherein G_2 is a group having a neutral or a net charge, selected from the following: $-CN(R_1R_2R_3)$, $-CN(R_1R_2)$, $-N[-](R_1R_2R_3)$, $-N[-](R_1R_2)$, or a heteroaryl group, wherein the heteroaryl is a ring having 5, 6 or 7 atoms, and wherein at least one atom of the heteroaryl is selected form the group consisting of a sulfur, a nitrogen, and an oxygen atom, wherein R_1, R_2 and R_3 independent of one another are selected from the group consisting of -H, $-CH_3$, $-CH_2CH_3$, or other linear alkyl groups such as propyl, butyl, or pentyl, wherein G_3 and G_4 independent of one another are selected from the group consisting of N, S, O, $(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkenyl, wherein X is a $(C_1\text{-}C_{12})$alkyl and wherein Z is present as a charged species when G_2 has a net charge, the charge of Z depends on the charge of G_2, Z is absent when G_2 is neutral in charge [in a pharmaceutically acceptable carrier.]; and

a pharmaceutically acceptable carrier.

2. (Thrice Amended) A pharmaceutical [tablet] composition comprising a pharmaceutically effective amount of N-ethyl-N'-(3-dimethylaminopropyl) urea or a salt thereof in combination with a pharmaceutically acceptable solid carrier.

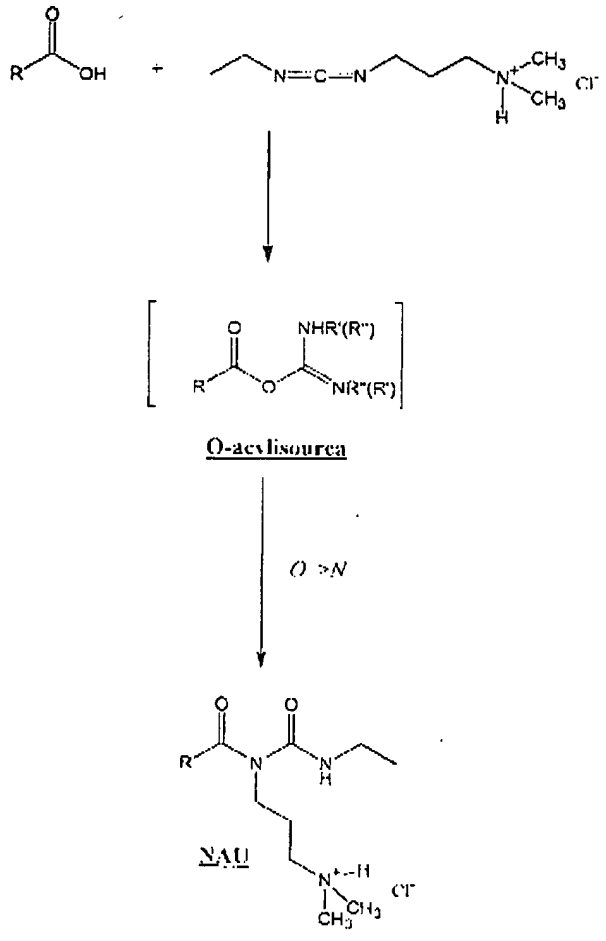
72. (Amended) A pharmaceutical [injectable] composition comprising a pharmaceutically effective amount of N-ethyl-N'-(3-dimethylaminopropyl) urea or a salt thereof in combination with a pharmaceutically acceptable sterile liquid carrier [for parenteral administration].

74. (Amended) A pharmaceutical [inhalable] composition comprising an aerosol form of a pharmaceutically effective amount of N-ethyl-N'-(3-dimethylaminopropyl) urea or a salt thereof [in combination with a pharmaceutically acceptable carrier for nasal administration].

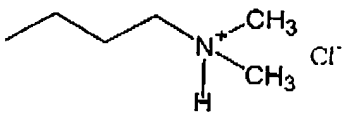
Once the pH of the aqueous HA mixture has been adjusted, a carbodiimide is admixed with the HA. Preferred carbodiimides include EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide or ETC (1-ethyl-3-(3-dimethylaminopropyl)) carbodiimide methiodide. EDC is soluble in water and is preferred.

The sequence and mode of addition of the reagents are not critical factors, but the ratio of the carbodiimide to HA is important. Best results are obtained when the ratio of carbodiimide to HA ranges from about 0.5:1 to 2:1. Lower ratios typically form more soluble products, while higher ratios typically result in soluble products.

In one embodiment, the derivatized HA/CMC gels of this invention are prepared by the reaction scheme shown below. As shown, HA/CMC is reacted with a derivatizing agent, such as the carbodiimide EDC, in the absence of a nucleophile.

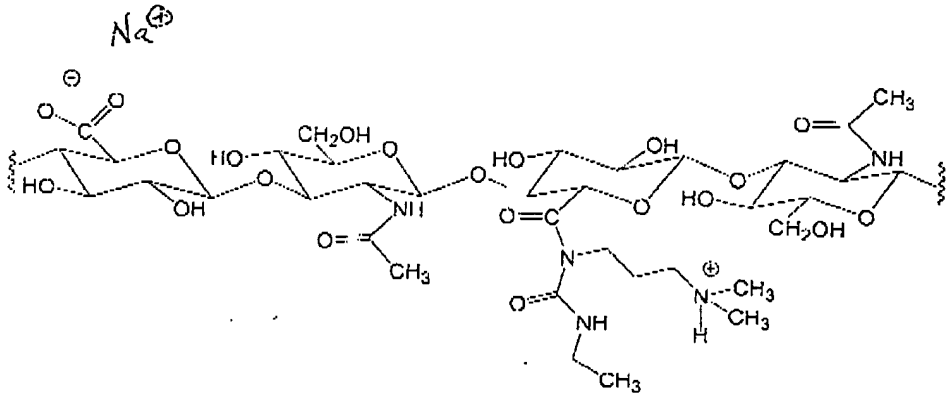


wherein R is HA or CMC, R' is Ethyl, and R" is

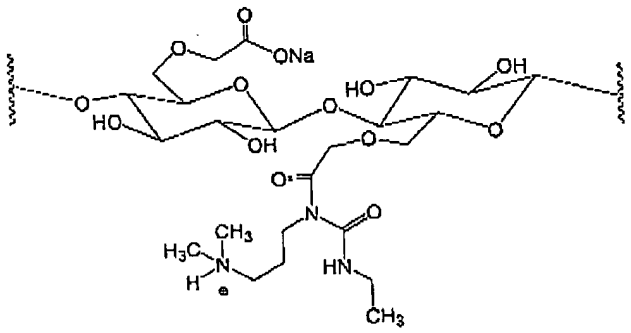


Normal reaction conditions can result in a 5% to 20% (molar basis) modification of the carboxyl groups on each polymer molecule. The carboxyl groups are both protonated and deprotonated, while the NAU modified groups are positively charged.

An exemplary diimide modified hyaluronic acid molecule is shown below:



An exemplary diimide modified carboxymethylcellulose molecule is shown below:



C6 cont.

The reaction product is a dried powder which can be dispersed in a buffered solution or physiological saline at concentrations of between 1% and 6% by weight. The product is capable of being terminally sterilized, which facilitates its storage and handling.

One particularly useful derivatized gel product is Seprafilm®, a proprietary hyaluronic acid/carboxymethylcellulose gel product available from the Genzyme Corporation.

While not intending to be bound by any particular theory or mechanism, it is believed that the immunomodulating pharmaceutical compositions of the invention function in some aspects by inducing levels of IL-10. IL-10 is an anti-inflammatory cytokine that causes the down-regulation or inhibition of pro-inflammatory factors, cytokines, or cells. When the body encounters an inflammatory stimulus such as that which occurs with intra-abdominal infections, the elicitation of pro-inflammatory cytokines such as TNF-α is followed by the release of anti-inflammatory cytokines such as IL-10. IL-10 serves to dampen or mitigate the inflammatory process in order to maintain homeostasis and prevent excessive inflammation. In this manner, the invention provides methods for protecting against sepsis, adhesion formation, or excessive inflammation by the administration of each of these materials. It has also been discovered according to the invention that the immunomodulating pharmaceutical compositions of the invention function to prevent nitric oxide synthase (NOS) activity.

The anti-inflammatory effects of the compositions of the invention are particularly effective when the pharmaceutical composition is administered to the subject over a period of time. For instance, when the pharmaceutical compositions are slowly